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10/591,371	12/08/2006	Stefan Russwurm	3535.022	7019

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,371	RUSSWURM ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,10-25 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,10,16-21 and 34-38* is/are rejected.

7)☒ Claim(s) *6,11-15,22-25 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6, 8, 10-25 and 33-38 are pending and examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 09/09/2010.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Election/Restrictions

1. In the response of 11/09/2009, Applicant's elected the particular subcombination of RNAs of SEQ ID NO: 1-7, 9, 10, 78, 79, 81 and 87.

It is noted claim 33, drawn to the elected subcombination of RNAs, is only objected to in this Office Action. In the interest of customer service, the Examiner points out that any claims that require all of the elements of the allowed subcombination would be allowable subject matter. For example, Applicants may wish to write a claim that depends from claim 33 which recites "the method of claim 33, further comprising measuring the abundance of mRNA expressed from the FJ32987 gene comprising at least 20 contiguous nucleotides of SEQ DI NO: 13", where any of the genes of Table 2 may be recited.

Withdrawn Objection to the Specification

2. The objection to the specification, as set forth on page 3 of the Office Action of 03/09/2010, is **WITHDRAWN** in light of the amendments to the specification of 09/09/2010.

Withdrawn Claim Objections

3. The objection to claim 1, as set forth on page 3 of the Office Action of 03/09/2010, is **WITHDRAWN** in light of the amendments to the claims.

New Claim Objections

4. Claims 33, 37 and 38 are objected to because of the following informalities: In claim 33, part (iv) of the claim recites “at least 20t”, where the phrase “at least 20” is correct. Claims 37 and 38 recite the term "SEQ:ID No." where the term "SEQ ID NO: " is correct. Appropriate correction is required.

Withdrawn Claim Rejections – Claim 27 ‘Use’ claim

5. The rejections of claim 27 under 35 U.S.C. 112, second paragraph, and 35 U.S.C. 101, as set forth on pages 3-4 of the Office Action of 03/09/2010, are **WITHDRAWN** in light of the cancellation of claim 27.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

6. The rejections of claims 1-25 under 35 USC 112 2nd ¶, as set forth on pages 4-6 of the Office Action of 03/09/2010, are **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

7. Claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 3 are unclear over recitation in claim 2 of the phrases “the sample-RNA”, “the control-RNA” and “the DNA”, because there is no antecedent basis in the claims for any “sample-RNA”, “control-RNA” or “DNA".

Claim 3 is unclear over recitation of the phrase “the reference gene”, because there is no antecedent basis in the claim for any “reference gene”.

Claim 4 is unclear over recitation of the phrase “the sample-RNA”, because there is no antecedent basis in the claim for any “sample-RNA”.

Claim 5 is unclear over recitation of the phrase “the RNA”, because there is no antecedent basis in the claim for any “RNA” where the base claim (i.e. claim 33) recites only “mRNAs”.

Claim 8 is unclear because the claim depends from claim 7, where claim 7 is cancelled, and thus the required limitations of pending claim 8 are entirely unclear.

Claim 16 is unclear over the recitations "the gene or gene fragments" because there is no antecedent basis in the claim for any “gene or gene fragments”. Further,

claim 16 is unclear over recitation of the limitation "their RNA listed in claim 10", where claim 10 does not appear to recite any "RNA".

Claim 17 is unclear in so far as the claim recites “5-100” as a range of base pairs, which does not appear to be consistent with the requirements of claim 33, from which claim 16 is dependent, where claim 33 requires “at least 20 contiguous nucleotides” of each recited gene.

Claim 18 is unclear over recitation of the limitation “the detectable markers” because there is no antecedent basis in the claim for any “detectable markers”.

Claim 19 is unclear over recitation of the limitation “the detectable markers” because there is no antecedent basis in the claim for any “detectable markers”.

Claims 20 and 21 are each unclear over recitation of the phrase “the sampl-RNA and the control-RNA” as there is no antecedent basis for any “sample-RNA” or “control-RNA” in the claim.

Claims 34-38 are unclear over recitation of “Cy5vsCy3” and “Cy3vsCy5”, as recited in claim 34, with regard to parameters used to determine expression prominence in a diagnostic method. The limitations are unclear because there is no indication in the claims as to what sample is labeled with a particular marker, and as such the calculative methods to arrive at any ratio are completely undefined to the skilled artisan wishing to practice the method.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Scope of Enablement

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 10 and 34-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the subject matter of independent claim 33:

> A method for differentiating non-septic systemic inflammatory response syndrome (SIRS) from sepsis in a human subject, said method comprising:
>
> a. measuring the abundance of a plurality of mRNAs in a blood sample from said human subject; and
>
> b. comparing the abundance of the plurality of mRNAs in the blood sample from said human subject to the abundance of the plurality of mRNAs in blood samples from a control population of human subjects with non-septic SIRS;
>
> wherein the plurality of mRNAs comprises:
>
> (i) mRNA, expressed from the MAGED1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 1;
> (ii) mRNA, expressed from the H1F2 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 2;
> (iii) mRNA, expressed from the DEFA4 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 3;
> (iv) mRNA, expressed from the SLC2A1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 4;
> (v) mRNA, expressed from the IHPK1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 5;
> (vi) mRNA, expressed from the IGLL1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 6;
> (vii) mRNA, expressed from the FLJ12085 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 7;
> (viii) mRNA, expressed from the CA1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 9;
> (ix) mRNA, expressed from the ZAP70 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 10;
> (x) mRNA, expressed from the IGHM gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 78;
> (xi) mRNA, expressed from the KIAA0481 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 79;

(xii) mRNA, expressed from the IGKV1D-12 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 81; and
(xiii) mRNA, expressed from the KLF1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 87;

wherein an increased likelihood of the presence of sepsis in said human subject is determined when the abundance of the plurality of mRNAs in the blood sample from said human subject is statistically significantly greater than abundance of the plurality of mRNAs in blood samples from a control population of human subjects with non-septic SIRS.

does not reasonably provide enablement for the methods as claimed which broadly encompass diagnostic methods using control RNA from any sample source (i.e. non-blood) and that generically require any gene having an activity for distinguishing SIRS and sepsis and encompass any altered (i.e. more or less prominent) expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The rejected claims are drawn to methods for differentiating non-septic systemic inflammatory response syndrome (SIRS) and sepsis in a human subject comprising comparing a blood sample RNA to a control of control RNA from any body fluid source (e.g. blood, bodily excretions).

The claims generically encompass any gene that has an activity "for distinguishing between SIRS and sepsis" and any fragments of genes.

The claims encompass any detected difference (e.g. any amount of compared over expression or under expression) between a sample RNA and any control RNA.

Direction provided by the specification and working example

The instant specification teaches an example wherein gene expression is measured in post-operative subjects with systemic inflammation, and the same subjects at a later time wherein the systemic inflammation is caused by sepsis. As relevant to the Election, the instant specification teaches a statistically significant increase in the expression of mRNAs of comprised of SEQ ID NO: 1-7, 9, 10 78, 79, 81 and 87 in blood of the subjects after they have sepsis as compared to the same subjects with pre-septic SIRS.

The instant specification teaches only the analysis of human subjects, and does not teach the analysis of any non-human organisms.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the quantitative analysis of RNA samples is high, the level of unpredictability in correlating any particular expression level with a diagnosis of or prediction of sepsis is even higher.

Because the claims encompass any compared level of RNA (any difference in RNA amounts or any changes in RNA concentration), it is relevant to point out that Cheung et al (2003) (as cited on the IDS of 05/05/2009) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of *ACTG2* in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by

a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of a detected biomarker can in fact be indicative of sepsis or SIRS. This is particularly relevant where the claims generically encompass any genes or fragments (e.g. claim 1), and specifically include gene fragments with as few as 5 nucleotides of the Elected genes (e.g. claim 10). Similarly, Shalon et al (2001) (as cited on the IDS of 05/05/2009) teaches that preferably 20-50 different test individuals are assayed to obtain meaningful data showing a significant change in gene expression levels, and changes of gene expression of at least 2 fold and up to 100 fold or more are desirable for the comparison of gene expression levels between a case and control population (p.10 ¶156, ¶158).

Because the claims encompass comparing control-RNA from any body fluid source, it is relevant to point out the unpredictability with regard to the analysis of RNA profiles obtained from different sample types. Cobb et al (2002) teaches the analysis of gene expression in spleen and liver sample from septic mice. Notably, the reference teaches that, when compared to a non-septic sample, the relevant biomarker profiles of the septic mouse spleen and the septic mouse liver contain different biomarkers (Table 1; p.2714, middle col., lns.2-8). It is thus unpredictable as to how one might use any biomarker profile comprising biomarkers identified in a blood sample in the analysis of a control biomarker profile obtained from any other body fluid.

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention in the full scope as claimed. One would have to establish that a particular comparison (e.g. specific compared amount) of any

analyzed RNA may be indicative of an individual either being septic or becoming septic. Within the scope of the claims, this would require the analysis of control-RNA samples from different sources (e.g. blood, saliva, urine) to reliably determine the status of sepsis in the individual.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the paucity of working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Response to Remarks

Applicants' remarks (p.16 of the Remarks) have been fully and carefully considered but are not found to be persuasive to withdraw the rejection as set forth above. Applicants have argued that the claims have been amended to be limited to analyses requiring human blood samples and genes fragments of at least 20 nucleotides. As set forth in the rejection, the claims encompass the unpredictable aspects of any generic gene that is associated with sepsis or SIRS, where such an association between any of the 30,000 genes in a human subject and the required functionality of sepsis indication is unpredictable. Furthermore, the claims encompass analyses wherein any difference in gene expression (i.e. any amount of more or less prominent expression) is used in the diagnosis of sepsis, and also the claims still

encompass the comparison of a sample RNA with a control RNA from any tissue or body fluid source.

The rejection as set forth is **MAINTAINED.**

Double Patenting
Maintained in Part

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1 and 34-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 12-29 of copending Application No. 10/551,874. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the conflicting application are drawn to methods of diagnosing SIRS of sepsis, which would

accomplish the same goal as the claims of the instant application in differentiation SIRS from sepsis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 1 and 34-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 11/909,372. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the conflicting application encompass the detection of infections multiple organ failure in a subject, thus encompassing the diagnosis of sepsis in a subject which is the subject matter of the methods of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks

Applicants' remarks concerning the provisional double patenting rejections (p.17 of the Remarks of 09/09/2010) are noted. The provisional rejections as set forth above are **MAINTAINED.**

Conclusion

13. No claim is allowed.

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634